



Effect of Crack Cocaine Administration on the Histomorphology of the Brain and Testis in Adult Albino Wistar Rats

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International.



ABSTRACT

Crack cocaine, a potent free base form of cocaine that is smoked, is highly addictive and causes both physical and psychological dependence. Its use leads to significant health risks, including detrimental effects on the central nervous system and various organs, including the brain and testes. The aim of this study was to determine the histomorphological effects of crack cocaine on the brain and testis of adult albino Wistar rats. A total of forty (40) adult Albino Wistar rats were used, divided into four equal groups (A–D) of ten rats each. Group A served as the control, receiving only distilled water and feed. Groups B, C, and D were administered 0.5 ml, 2 ml, and 5 ml of crack cocaine extract, respectively, in addition to regular feed and water. The rats were treated daily for 14 days, and their body weights were monitored before and after treatment. The drug was administered orally. Histological examination of the brain revealed no significant alterations in tissue structure for the rats treated with crack cocaine, compared to the control group, indicating that under the study's conditions, crack cocaine did not induce noticeable histological changes in brain tissue

INTRODUCTION

Crack cocaine, often referred to simply as crack or rock, is a free base form of cocaine that is smoked to deliver its intense effects. As one of the most addictive substances known, crack cocaine has severe and wide-reaching consequences for both individuals and society. Unlike powdered cocaine, which is typically snorted or injected, crack cocaine is heated to produce a vapour that is inhaled, which intensifies its addictive potential. When smoked, crack induces a rapid and intense euphoria that has a short duration, but this fleeting high is often accompanied by dangerous physical, psychological, and social effects (1). Crack cocaine is regarded as one of the most potent forms of cocaine, primarily due to its ability to quickly enter the bloodstream through the lungs, which then leads to immediate brain stimulation (2). The intensity of crack cocaine's effects contributes significantly to its widespread abuse, making it a major public health crisis with far-reaching societal consequences (3).

The addiction to crack cocaine is driven by its ability to produce powerful changes in brain chemistry. When smoked, the drug crosses the blood-brain barrier rapidly, where it stimulates the release of neurotransmitters like dopamine, serotonin, and norepinephrine. These neurotransmitters play a crucial role in mood regulation, pleasure, and arousal, which accounts for the intense feelings of euphoria and heightened sensory perception users experience (4). While the euphoria is short-lived, the physiological impact of the drug remains much longer, leading to persistent cravings and intense addiction (5). The abuse of crack cocaine often results in significant neurobiological changes, such as neurodegeneration, synaptic dysfunction, and alterations to brain structures associated with reward, memory, and motivation (6). These alterations explain the long-term behavioral and cognitive impairments seen in chronic crack cocaine users, including memory deficits, poor impulse control, and heightened susceptibility to anxiety and depression (7).

Understanding the precise mechanisms behind crack cocaine's addictive properties is critical to developing effective treatment strategies and interventions. While much has been learned about the general effects of cocaine on the brain, research on crack cocaine, specifically its more potent form, is still in its infancy. The complexities of how crack cocaine alters brain structure and function at a cellular level remain a crucial area of exploration, as it is only through such insights that researchers can develop targeted therapies that may aid in addiction treatment and prevention (8).

Cocaine, as a substance, is derived from the leaves of the coca plant (*Erythroxylum coca*), native to the Andes mountains in South America. For centuries, indigenous populations used coca leaves for medicinal and ritualistic purposes due to their stimulant properties (9). It wasn't until the 19th century that cocaine was isolated and later utilized as a local anesthetic, a use that persists to this day in certain medical fields, such as dentistry and ophthalmology (10). However, as the recreational use of cocaine gained popularity, it quickly became associated with abuse and addiction. In its powdered form, cocaine can be snorted or dissolved for intravenous use. It wasn't until the 1980s that the smokable form of cocaine—crack cocaine—became prevalent, which led to an

explosion in its abuse and subsequent social problems (11). The “crack epidemic” in the U.S. during the late 20th century led to a wave of criminalization, stigmatization, and significant public health challenges (12).

The method of ingestion plays a crucial role in the drug’s potency. When heated and smoked as crack, the drug reaches the brain almost instantaneously, creating a quick and intense “high” that is much shorter than the effects of snorted cocaine. This rapid onset of action is what makes crack cocaine particularly addictive, with users often seeking repeated use to sustain the brief euphoric effects (13). The physiological and psychological impact of crack cocaine abuse is profound, as it leads to numerous short- and long-term health problems, including neurological impairments, cardiovascular complications, and reproductive system dysfunction (14).

A critical focus of this study is to understand the histomorphological effects of crack cocaine on the brain and testes of adult albino Wistar rats. Wistar rats are commonly used in biomedical research due to their well-documented physiology, genetics, and ease of handling. Their use in studying the effects of substances like crack cocaine is well-established, allowing researchers to extrapolate findings to potential human applications (15). This study aims to provide a detailed investigation into the cellular and tissue-level changes induced by crack cocaine exposure, focusing specifically on the brain and testes – two organs that play pivotal roles in the central nervous system and reproductive system, respectively.

By investigating these histological effects, the research will fill a significant gap in existing literature, especially with respect to the unique impact of crack cocaine as a more potent form of the drug. Given that most studies have focused on the broader effects of cocaine, crack cocaine’s specific impact on brain tissue and male reproductive health has not been well understood. The goal of this research is to explore these effects in-depth and contribute to the development of interventions that may help mitigate the harm caused by crack cocaine abuse (16).

LITERATURE REVIEW

The neurobiological and histological effects of cocaine, including crack cocaine, have been well-documented in scientific literature, particularly in relation to brain and reproductive health. However, while cocaine’s general impact on the central nervous system (CNS) has been extensively studied, there remains a limited understanding of how crack cocaine specifically affects brain tissue at the histological level. Cocaine abuse has been shown to cause significant neurodegeneration, particularly in areas of the brain responsible for reward processing and memory, such as the prefrontal cortex, hippocampus, and striatum (17). These regions are crucial for controlling emotional responses, decision-making, and motor functions, which explains the cognitive and behavioral impairments seen in chronic cocaine users (18). While powdered cocaine has been shown to cause damage to these areas, crack cocaine, being a more potent form, is likely to have more rapid and severe effects, leading to faster onset neurotoxicity and potentially irreversible brain damage (19).

Several studies have also addressed the reproductive toxicity of cocaine, particularly its effects on male fertility. Cocaine, whether in its powdered or crack form, has been demonstrated to interfere with spermatogenesis (the production of sperm), reduce testosterone levels, and alter the histology of testicular tissue (20). This interference can result in fertility issues, hormonal imbalances, and other reproductive dysfunctions, including changes in the structure of the seminiferous tubules and Leydig cells within the testes (21). Studies in rats have shown that crack cocaine leads to significant structural damage in testicular tissues, which can affect the male reproductive system's ability to produce both sperm and male sex hormones (22). The specific effects of crack cocaine on testicular tissue in male Wistar rats, however, have not been sufficiently studied, and this represents an important gap in the literature.

In addition to the damage caused by crack cocaine on the brain and reproductive system, the question of gender differences in response to cocaine abuse is of increasing interest. Research suggests that female rats may exhibit greater sensitivity to the reinforcing effects of cocaine compared to males (23). This difference could be due to the hormonal influences that affect neural circuits involved in reward processing and addiction. For example, estrogen has been shown to enhance dopamine release in certain areas of the brain, making females more susceptible to the euphoric effects of the drug (24). As such, exploring gender-specific responses to crack cocaine in rats could help inform personalized treatment strategies for addiction, which would take into account the unique biological and hormonal differences between males and females (25).

Despite the growing body of research on cocaine's effects, much of the literature has focused on the broader spectrum of cocaine's physiological and neurobiological consequences, with relatively few studies investigating the histological changes caused by crack cocaine in specific tissues such as the brain and testes. This gap in the literature is particularly concerning given the widespread abuse of crack cocaine and its serious health consequences. By examining the histopathological alterations in the brain and testes of Wistar rats, this study will provide valuable new insights into the mechanisms of addiction and the long-term effects of crack cocaine abuse, potentially informing the development of more effective addiction treatments (26). Furthermore, this research will have significant implications for public health, as it can aid in the design of interventions that target the specific neurobiological and reproductive harms caused by crack cocaine use (27).

while extensive research has been conducted on cocaine's general effects, there remains a notable gap in the literature regarding the specific histomorphological effects of crack cocaine, particularly in the context of male reproductive health and brain structure. By addressing this gap, this study aims to contribute crucial data that can help inform more effective treatment strategies and preventative measures for crack cocaine addiction (28). The findings will also highlight the importance of considering both neurobiological and reproductive factors when evaluating the broader societal impact of crack cocaine use.

METHODOLOGY

Experimental Animals/Housing Condition

Forty (40) Adult Albino Wistar rats of comparable sizes and weights were procured from the animal house and transferred to the experimental site where they were allowed two (2) weeks of acclimatization. They were housed in well ventilated labeled wooden cages at the site of the experiment. The cages was designed to secure the animals properly especially from wild animals/insects and cleaned daily. During this period of acclimatization, the rats were fed growers' mash and water provided *ad libitum*. Animals were maintained and experimental procedures complied with the guide for care and use of laboratory animals (National Research Council, 1985).

Experimental Design

A total of forty (40) adult Albino Wistar rats of comparable sizes were used for this study. They were divided into four equal groups (A – D) with ten (10) rats each. Group A served as the control and the rats were given distilled water and feed only. In addition to feed and water, groups B rats were given 0.5ml *crack cocaine extract* and *crack cocaine extract*, group C rats were given 2ml *crack cocaine extract*, and group D rats were given 5ml *crack cocaine extract* respectively. The drug administration was given daily for 14 days (2 weeks) and the weights of both the test and control animals was monitored before and after administration of *crack cocaine extract*. After the administration, the rats were put under light chloroform anaesthesia and the lungs were obtained. ANOVA was used to analyze the results of the weight and differences was considered significant at $p < 0.05$ level of confidence. All data was expressed in table as mean $\pm$ standard deviation (SD).

Animal Grouping

The experimental animals were separated into four groups (A – D). Group A had ten rats ($n = 10$) while groups B – D had ten rats ($n = 10$) each using 4 big cages to house them. Group A served as the control and received only the normal feed (grower's mash) and water with no administration of *crack cocaine extract*, while Group B, C and D received different doses of *crack cocaine extract* and were equally fed with grower's mash and water.

Study Duration

The preliminary studies, animal acclimatization, drug procurement and preparation, actual animal experiment and evaluation of results, lasted for a period of three months. However, the actual experiment lasted for lasted for four (4) weeks: two weeks of acclimatization and two weeks administration of *crack cocaine extract* to the test animals.

Collection and Identification of Plant Materials

Fresh prepared aqueous *crack cocaine extract* were collected from a health facility. The aqueous *extracts* were identified and authenticated by experts.

Preparation of Plants Extract

The powder *crack cocaine* was weighed using the electric weighing scale and 100g was dissolved in 1 litre of distilled water and stirred at intervals for 24 hours (1 day). This was later reconstituted to give the required doses of 0.5ml, 2ml and 5ml used in the present study.

Administration of Substance

Crack cocaine extracts was prepared to prepare the doses of 0.5ml, 2ml and 5ml respectively for the experiment. The administration of the *crack cocaine* extracts was given orally as follows:

- **Group A** (Control) received only normal feed (growers' mash) and distilled water daily for 28days.
- **Group B** received 0.5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.
- **Group C** received 2ml of *crack cocaine* extracts, feed and distilled water daily for 28days.
- **Group D** received 5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.

Ethical Approval

Ethical approval for the use and collection of samples from laboratory animals was obtained from the Ethics and Review Committee, College of Medical Sciences, Ambrose Alli University, Ekpoma.

Ethical Consideration (Ref No: AAU/HREC/25/1034) ,and was carried out in strict accordance with the guidelines for the care and use of animals for the research committee which is in line with that set by WHO.

Sample Collection and Analysis

Weight was measured before and after acclimatization. Similar weight measurements were done at the end of the treatment periods and the average weight recorded accordingly. Furthermore, the testis and brain of each rat was obtained at the end of the experiment under chloroform anaesthesia and fixed in 10% formalin for histological processing.

Processing Schedule

The tissues were processed according to standard histological procedures. The fixed plastic cassette tissues in 10% formalin were automatically processed by passing them through different grades of alcohol as follows:

70% alcohol	2hrs
80% alcohol	2hrs
90% alcohol	2hrs
90% alcohol	2hrs
95% alcohol	2hrs
Absolute	2hrs
Xylene 1	2hrs
Xylene II	2hrs
Molten paraffin wax 1	2hrs
Molten paraffin Wax II	2hrs

After the last timing, the tissues were removed from their plastic cassettes and placed at the centre of the metallic tissue mould and then filled with molten paraffin wax. They were left to solidify after which they were placed in the refrigerator at 5°C for 15 minutes. After the blocks were cool in the refrigerator for the time stated above, the blocks were removed from the metallic case using a knife and after which the paraffin wax at the side of the blocks were removed. The blocks were trimmed and cut serially at 3nm on a rotary microtome. The sections were floated in water bath at 55°C and picked up by the use of a clean frosted end slides. The frosted end slides were placed on the hot plate for 40 minutes for adequate attachment of the sections on the slides after which the sections were de-waxed, hydrated, air dried and stored in a slide box ready for staining.

Staining Procedure

Sections for general tissue structure were stained using Haematoxylin and Eosin staining technique.

1. The sections were de-waxed in 3 changes of xylene 5 minutes
2. The sections were hydrated through descending grades of alcohol (absolute, 95%, 80% and 70%).
3. The sections were stained in Harris haematoxylin 5 minutes
4. The sections were rinsed in running tap-water to remove excess stain
5. The sections were differentiated in 1% acid alcohol 3 seconds
6. The sections were blued in running tap water 10 minutes
7. The sections were counterstained with 1% eosin 1 minute
8. Sections were finally rinsed in water, dehydrated in ascending grades of alcohol (70%, 80, 95% and absolute)
9. The sections were cleared in xylene, air-dried and mounted with dibutylphthalate propylene xylene (DPX) (Armstrong *et al.*, 2007).

The slides were examined under a light microscope at x100 magnification and photomicrographs were taken.

Data Analysis

All results were expressed as mean $\pm$ standard deviation ($X \pm SD$). The obtained data was subjected to statistical analysis using SPSS (version 21). The test groups' values were compared with the values of the control group using One-way analysis of variance (ANOVA) at 95% level of confidence. Values of $P < 0.05$ were considered significant

RESULT

Table 1 shows the body weight changes of rats in the test and control groups. The results were presented in mean $\pm$ standard deviation. At every stage of the weight determinations, the control group (Group A) presented body weight gain at first, second, third and final week after acclimatization, while the test groups (B, C and D) presented body weight loss in the different weeks after acclimatization respectively. Though, the difference in weight didn't show any significant difference ($p>0.05$) within the test groups, group D was observed to have a higher weight reduction, followed by group C and B respectively. The body weight of control animals (group A) before acclimatization and before sacrificing was 205.50 ± 0.50 g and 245.25 ± 0.50 g. Similarly, the body weight of the test animals in group B before acclimatization and before sacrificing was 215.50 ± 1.00 g and 200.55 ± 2.22 g, group C was 210.40 ± 1.29 g and 195.25 ± 3.24 g, group D was 225.55 ± 1.41 g and 190.25 ± 2.45 g respectively.

Table 1. Body Weight Changes of Rats at Various Intervals

<i>Weight (g)</i>	<i>Control</i> <i>(n = 10)</i>	<i>B (100mg)</i> <i>(n = 10)</i>	<i>C (200mg)</i> <i>(n = 10)</i>	<i>D (300mg)</i> <i>(n = 10)</i>
WBA	210.50 ± 0.50	220.50 ± 1.00	215.40 ± 1.29	230.55 ± 1.41
WAA	220.65 ± 0.50	217.75 ± 1.50	210.50 ± 0.42	225.45 ± 1.20
W2WK	225.45 ± 0.50	215.25 ± 1.35	205.85 ± 1.50	215.50 ± 1.84
W3WK	240.15 ± 1.71	210.50 ± 1.50	205.50 ± 1.15	205.35 ± 2.55
FW	250.25 ± 0.50	205.55 ± 2.22	200.25 ± 3.24	195.25 ± 2.45

KEY:

WBA: Weight before acclimatization

WAA: Weight after acclimatization

W2WK: Weight at second week of cocaine extracts

W3WK: Weight at third week of cocaine extracts

FW: Final weight before sacrificing

Values are mean $\pm$ Standard deviation; Wt= weight (Grams);

n: Number of sample.



Figure 1. Testis Control X100

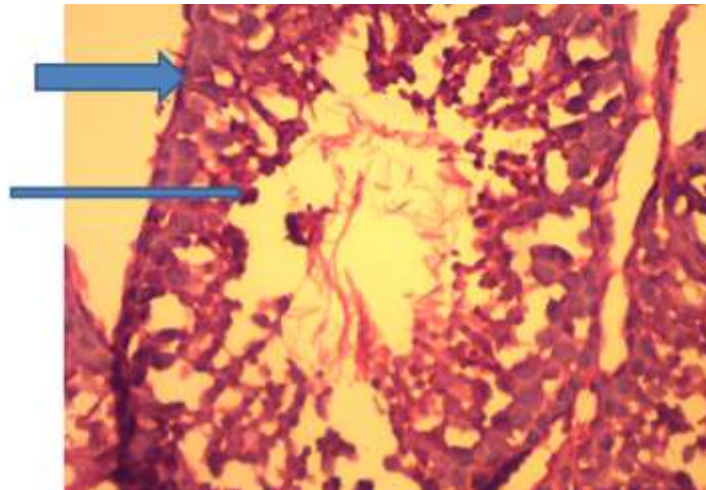


Figure 2. Testis Control X400: Section of the Testis Showing Spermatozoa (Thin Arrow) and Sertoli Cells (Thick Arrow)

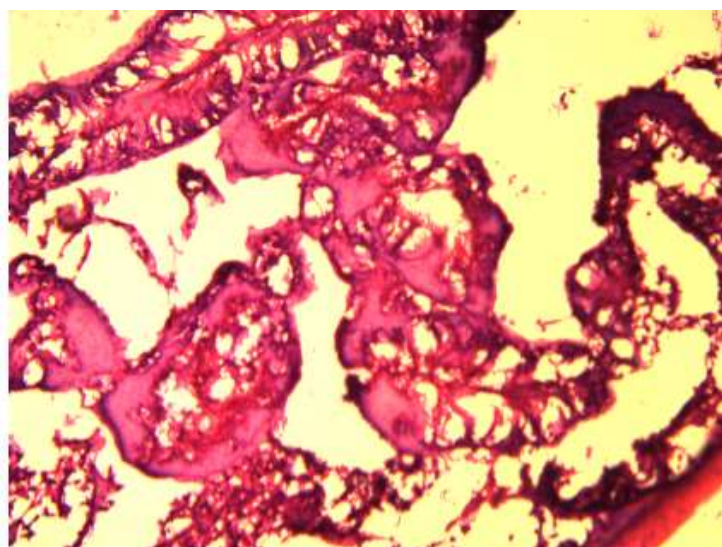


Figure 3. Testis GP2 X100

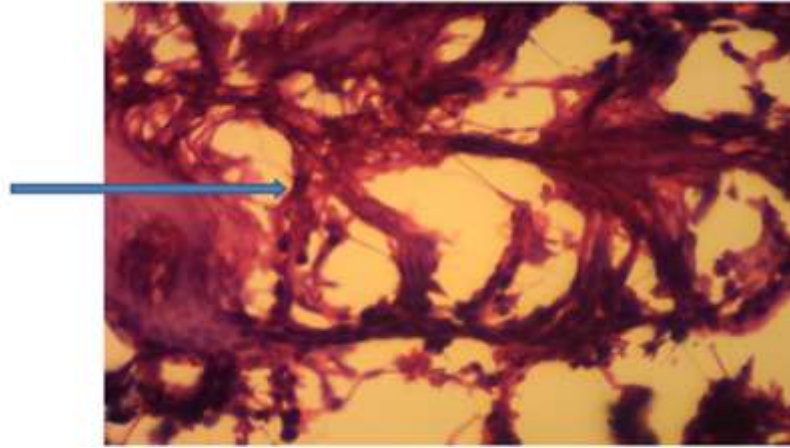


Figure 4. Testis GP2 X400: Section of the Testis Shows a Partially Effaced Architecture of the Seminiferous Tubules Composed Predominantly of Fibroconnective Tissue and Very Scant Cellular Elements. No Spermatozoa Seen

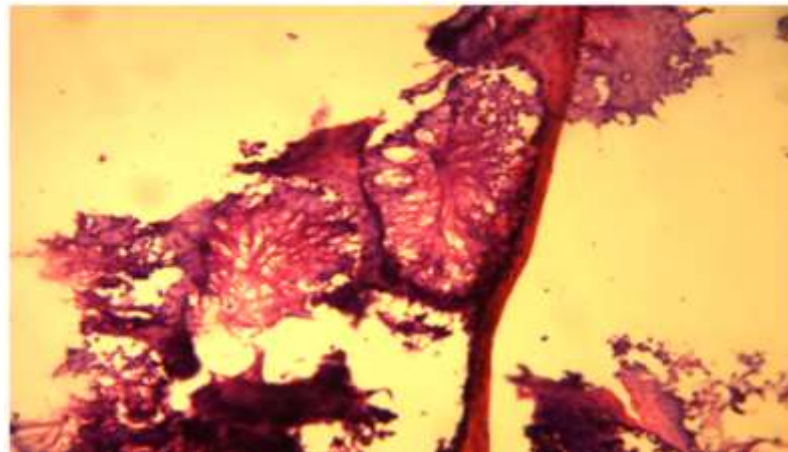


Figure 5. Testis GP3 X100

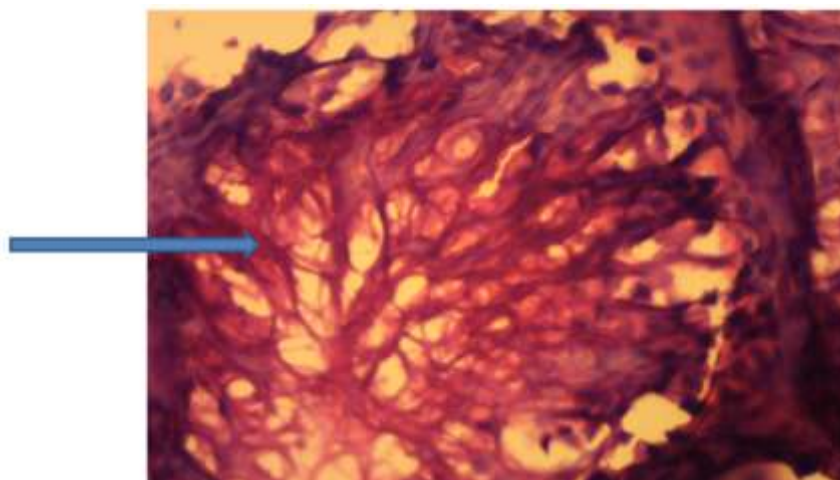


Figure 6. Testis GP3 X400: Section of the Testis Shows a Partially Effaced Architecture of the Seminiferous Tubules Composed Predominantly of Fibroconnective Tissue (Arrow) and Scant Cellular Elements. No Spermatozoa Seen

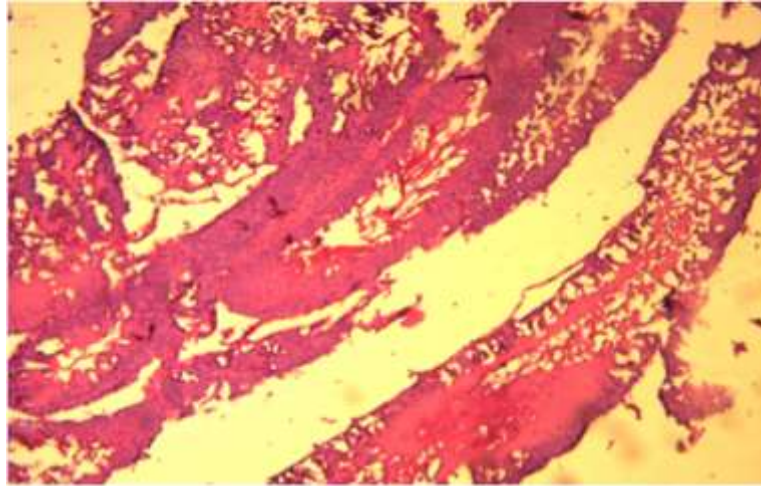


Figure 7. Testis GP4 X100

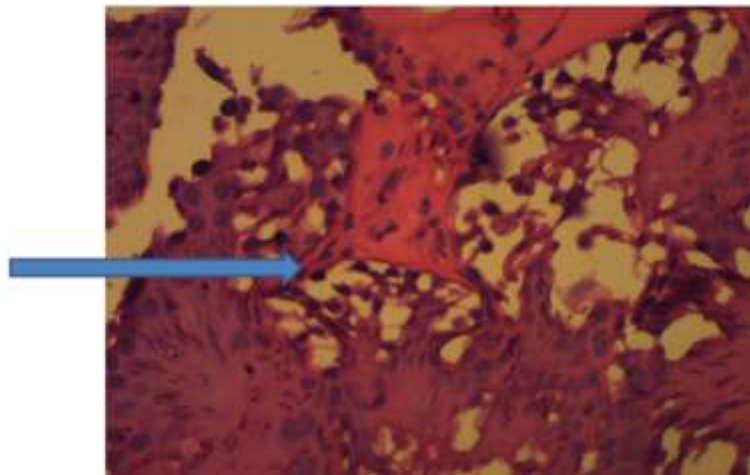


Figure 8. Testis Gp4 X400: Section of the Testis Shows a Partially Effaced Architecture of the Seminiferous Tubules Composed Predominantly of Fibroconnective Tissue and Scant Cellular Elements

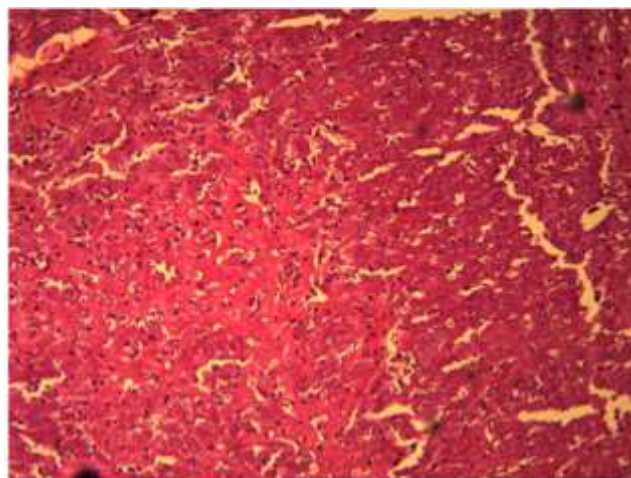


Figure 9. Brain Control X100

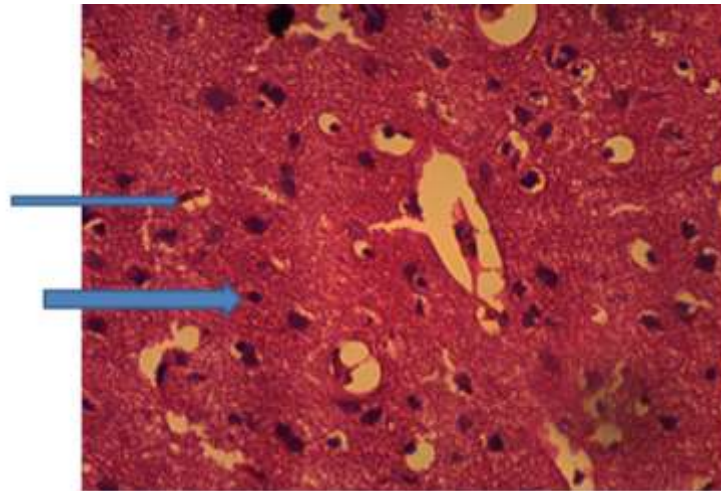


Figure 10. Brain Control X400: Section of the Brain Shows Normal Neuron (Thin Arrow) and Normal Glial Cell (Thick Arrow)

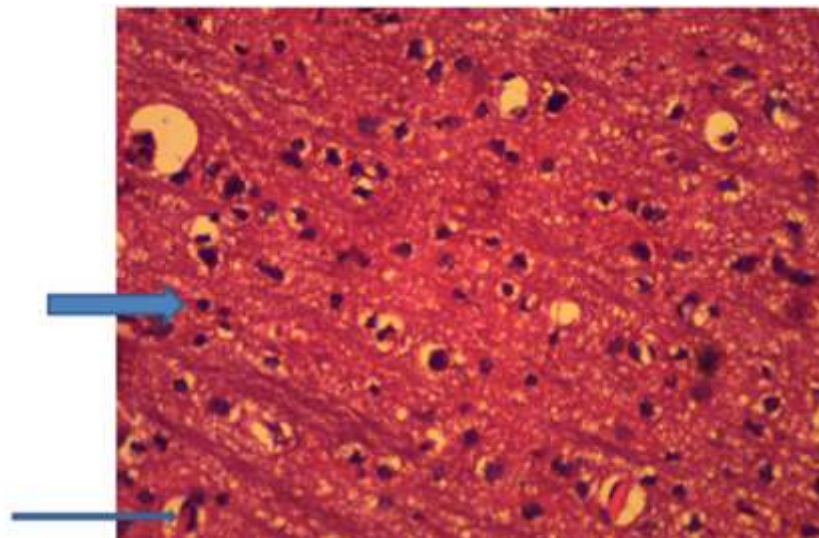


Figure 11. Brain A X400: Section of the Brain Shows Normal Neuron (Thin Arrow) and Normal Glial Cell (Thick Arrow)

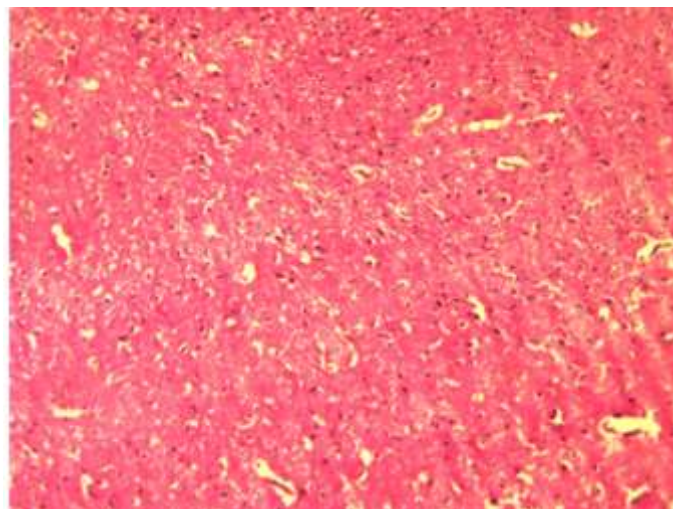


Figure 12. Brain B X100

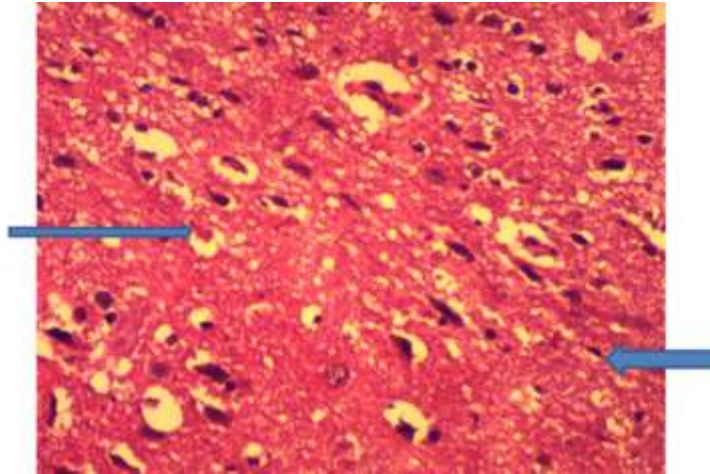


Figure 13. Brain B X400: Section of the Brain Shows Normal Neuron (Thin Arrow) and Normal Glial Cell (Thick Arrow)

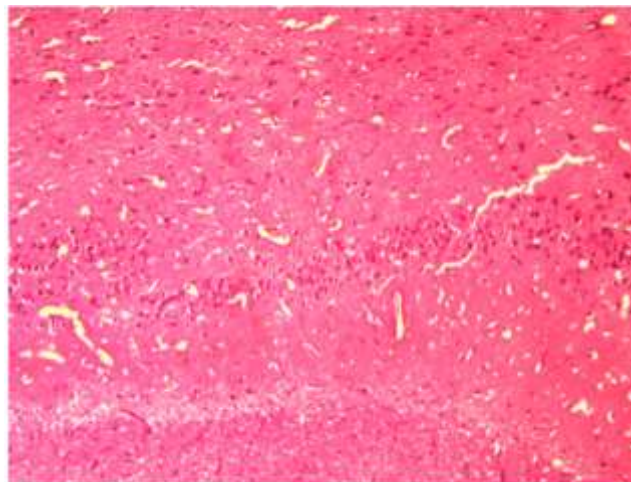


Figure 14. Brain C X100

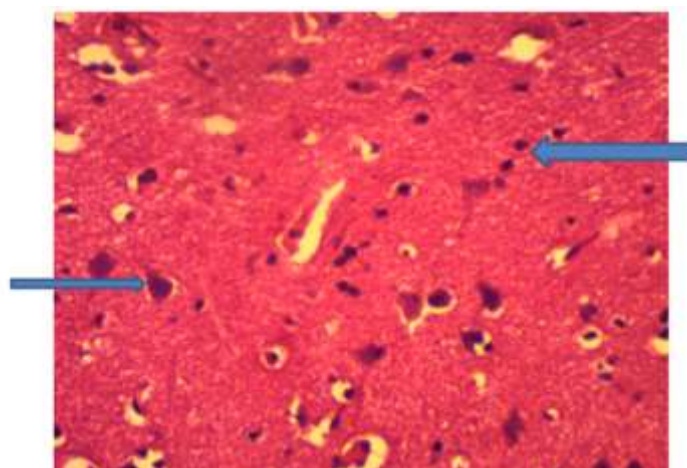


Figure 15. Brain C X400: Section of the Brain Shows Normal Neuron (Thin Arrow) and Normal Glial Cell (Thick Arrow)

DISCUSSION

Cocaine is a potent stimulant derived from the leaves of the coca plant (*Erythroxylum coca*), native to South America. Indigenous populations have long used coca leaves for medicinal purposes, such as combating altitude sickness and enhancing energy levels. Cocaine, in its refined form, can be found as a crystalline powder (powder cocaine) or as small rocks (crack cocaine) that are smoked (28). Crack cocaine, a more potent derivative of cocaine, is created by processing powder cocaine with baking soda or ammonia. This results in a form of cocaine that is smoked, delivering a rapid and intense high (29).

Cocaine's physiological effects are wide-ranging, with significant impacts on the central nervous system, cardiovascular system, and metabolism. It is widely recognized for suppressing appetite, leading to decreased food intake and subsequent weight loss. However, this study found no significant alterations in body weight in rats administered varying doses of crack cocaine. These findings contradict those of (30), who found significant reductions in fat mass in cocaine-dependent individuals compared to non-users, suggesting that cocaine usage perturbs fat regulation and metabolism.

Several studies have shown that chronic cocaine use can negatively affect brain structures and functions. Cocaine has been found to reduce dendritic spine density, impair synaptic plasticity, and disrupt the communication between neurons in the brain (31). These changes can lead to long-term cognitive deficits, including impaired learning and memory. In contrast, the histological analysis in this study showed no significant damage to the brain tissue in Wistar rats exposed to cocaine. These results contrast with findings by (32), who observed alterations in the prefrontal cortex and hippocampus of mice exposed to low doses of cocaine, which included gliosis and ischemic tissue necrosis. Their findings suggest that even low doses of cocaine can cause subtle, yet significant, histological changes in brain structures that may not manifest in immediate behavioral or metabolic changes.

White matter, which is crucial for the efficient transmission of nerve impulses across the brain, also shows altered integrity in cocaine users. In human studies, cocaine use has been associated with changes in the white matter of the anterior corpus callosum, which is vital for interhemispheric communication. (33) reported a reduction in myelin basic protein and an increase in neurofilament expression, which is consistent with a loss of white matter integrity in cocaine-dependent individuals. This study did not observe any similar alterations in the brain tissue of the experimental rats, suggesting that short-term or low-dose exposure might not result in the same degree of damage observed in humans (34).

In the testes, cocaine use led to significant histological alterations. The seminiferous tubules showed signs of degeneration, with a marked increase in fibroconnective tissue and the absence of spermatozoa, consistent with the findings of (35) and (36), who reported similar disruptions in spermatogenesis and seminiferous tubule structure in rats exposed to cocaine. Cocaine's effects on the testes may be attributed to hormonal disruptions, particularly the impairment of testosterone production by Leydig cells, which is essential for

normal spermatogenesis (37) and (38). Additionally, oxidative stress, vasoconstriction, and inflammation likely contribute to the observed testicular damage (39) and (40).

CONCLUSIONS

Cocaine's impact on the histology of both the brain and the testes is complex and can vary based on several factors, including dose, duration of exposure, and the individual's susceptibility. While no significant histological changes were observed in the brain tissue of the experimental animals in this study, cocaine has the potential to cause subtle neurobiological changes that may not always be apparent at the histological level. In contrast, cocaine's effects on the testes were more pronounced, resulting in significant damage to seminiferous tubules and disruption of spermatogenesis. This damage likely stems from a combination of hormonal imbalances, oxidative stress, and direct toxic effects on testicular tissue.

RECOMMENDATIONS

1. **Public Health Campaigns on Cocaine Use:** It is critical to raise awareness about the long-term effects of cocaine on both the brain and reproductive systems. Public health campaigns should emphasize that even if immediate histological changes are not observed, cocaine can cause subtle and cumulative damage over time, especially to vital systems like the brain and reproductive organs.
2. **Comprehensive Treatment Programs:** Governments and healthcare organizations should implement accessible, holistic treatment programs for cocaine addiction. These programs should address the physical, psychological, and reproductive health aspects of addiction, offering support to individuals who seek recovery.

FURTHER STUDY

This study still has limitations so that further research is needed on the topic of the Effect of Crack Cocaine Administration on the Histomorphology of the Brain and Testis in Adult Albino Wistar Rats to perfect this study and increase insight for readers and authors.

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